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GRANT NUMBER DAMD17-97-1-7279

TITLE: Correlative Study of Tumor Hypoxia and Metastatic Potential in Breast Cancer

PRINCIPAL INVESTIGATOR: Mahesh A. Varia, M.D.

CONTRACTING ORGANIZATION: University of North Carolina
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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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**13. ABSTRACT** *(Maximum 200 words)*

**Purpose:** We propose a novel physiological approach using tumor hypoxia assessment to study the metastatic potential of primary breast cancer cells. Does the presence of hypoxia in breast primary detected by pimonidazole immunohistochemical binding, correlate with the presence of axillary lymph node metastases, and correlate the presence of hypoxia with markers of cell proliferation, p53, apoptosis, and VEGF in the primary breast tumor tissue.

**Scope:** The specific aims are:

**I:** Determine the presence and extent of tumor hypoxia in biopsies of primary breast cancer using pimonidazole binding to hypoxic tumor cells.

**II:** Determine the patterns of pimonidazole binding in the breast cancer biopsies in relation to other landmarks such as blood vessels and necrosis.

**III:** Correlate the presence and extent of tumor hypoxia in primary breast cancer with the presence of axillary node metastases.

**IV:** Correlate the presence and extent of tumor hypoxia with the presence of other biological markers: p53, apoptosis, PCNA, Ki-67, and VEGF.

**V:** Monitor adverse effects of pimonidazole.

**Major Findings:** The clinical protocol has not been initiated. Please see the Annual Report Statement.

We request deferral of the start date of the clinical research protocol to November 1st, 1998 or earlier pending Review Committee approval.

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__✓__ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Mahesh Varma 9.28.98

PI - Signature Date

# Annual Report for Grant DAMD17-97-1-7279

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September 28, 1998

**For Attention of MCMR-RMI-S**
**Research Data Management**
**SUBJECT: Annual Report for Grant DAMD17-97-1-7279**

Ms. Judy Pawlus
Office of the Deputy Chief of Staff for Information Management
U.S. Army Medical Research and Materiel Command
504 Scott Street,
Fort Detrick, MD 21702-5012

Dear Ms. Pawlus,

Enclosed please find the following in reference to the Annual Report for Grant DAMD17-97-1-7279.

1. Front Cover
2. Standard Form 298
3. Foreword
4. Table of Contents
5. Annual Report Statement

Please note that this research project has been delayed on account of issues related to the Consent for Human Subjects as described in the Annual Report Statement and we are hoping to commence patient entry this fall for research on this grant.

**Request for Deferral of Protocol Start Date:** We request a deferral of the start date of the clinical research protocol to November 1st, 1998 or earlier pending Reveiew Committee approval.. This should complete all the required approvals of the involved Human Research Review Boards and adherence to policies of applicable Federal Law 45 CFR 46. Explanation for this request is provided in the attached Annual Report Statement.

Sincerely,

Mahesh A. Varia

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Enc.

## Annual Report Statement

## Grant DAMD17-97-1-7279

There has been a lag in obtaining the approval of the Informed Consent Form for participation by breast cancer patients on the research study funded by this grant. After the initial award of the grant, a number of changes in the Consent Form approved by our Institutional Review Board were requested by the Surgeon General's Human Subjects Research Review Board (HSRRB, HURRAD Log. No. A-7766), USAMRMC Human Subjects Protection Division.

Although most of these changes could be addressed without significant difficulty, a major problem related to provision of financial compensation for research subjects in the event of research related **injury**. The required language of the two Review Boards were in direct conflict. In the Consent Form, our Review Board requires that in such a situation, provision will be made for medical care to the research subject but the institution cannot assume financial responsibility. HSSRB required that provision be made of financial responsibility. According to the Senior Legal Counsel of the University of North Carolina, the State of North Carolina does not permit the University to assume such responsibility.

After further discussions on this subject, language acceptable to both Review Boards was developed whereby Department of Defense as the sponsor of the research assumes the financial responsibility. These deliberations and required approval of the Consent Form has delayed entry of research subjects entry into the research protocol for this grant.

Pending final clarifications to the Clinical Research Advisory Committee our General Clinical Research Center (GCRC) regarding the cost of the research component of the tumor biopsy procedure, full approval of the clinical protocol is anticipated at the Committee's next meeting next month. The GCRC has indicated its enthusiastic approval of the protocol and unanimous support of the research proposal.

In view of the above deliberations and in order to comply with the requirements of the Human Research Review Boards of the DOD, University of North Carolina, and the GCRC, we have not embarked on the enrollment of patients.

**Request for Deferral:** We request a deferral of the start date of the clinical research protocol to November 1st, 1998 or earlier as expected with the GCRC approval. This should complete all the required approvals of the involved Human Research Review Boards and adherence to policies of applicable Federal Law 45 CFR 46.

We are extremely excited and enthusiastic about this innovative research and are very anxious to proceed with patient enrollment in compliance with the applicable approvals.

Revised, 9/30/98.